HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.
AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

AFINITOR is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. (1)

DOSAGE AND ADMINISTRATION

- 10 mg once daily with or without food. (2.1)
- Treatment interruption and/or dose reduction to 5 mg once daily may be needed to manage adverse drug reactions. (2.2)
- For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg tablets with no score. (3)

CONTRAINDICATIONS

Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.4)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.7)
- Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.8, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥30%) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Strong and moderate CYP3A4 or PgP inhibitors: Avoid concomitant use. (5.5, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2.2, 7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: AFINITOR should not be used in patients with Child-Pugh class C hepatic impairment. For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg daily. (2.2, 5.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose
2.2 Dose Modifications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Non-infectious Pneumonitis
5.2 Infections
5.3 Oral Ulceration
5.4 Laboratory Tests and Monitoring
5.5 Drug-drug Interactions
5.6 Hepatic Impairment
5.7 Vaccinations
5.8 Use in Pregnancy
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
7 DRUG INTERACTIONS
7.1 Agents that may Increase Everolimus Blood Concentrations
7.2 Agents that may Decrease Everolimus Blood Concentrations
7.3 Agents whose Plasma Concentrations may be Altered by Everolimus
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Non-infectious Pneumonitis
17.2 Infections
17.3 Oral Ulceration
17.4 Laboratory Tests and Monitoring
17.5 Drug-drug Interactions
17.6 Hepatic Impairment
17.7 Vaccinations
17.8 Pregnancy
17.9 FDA-approved Patient Labeling

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of AFINITOR for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily at the same time every day, either with or without food *[see Clinical Pharmacology (12.3)]*. AFINITOR tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.
Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

2.2 Dose Modifications

Management of severe and/or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is 5 mg daily *[see Warnings and Precautions (5.1)]*.
Hepatic Impairment: For patients with moderate hepatic impairment (Child-Pugh class B), reduce the dose to 5 mg daily. AFINITOR has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this patient population *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.
Strong CYP3A4 Inducers: Avoid the use of concomitant strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). If patients require co-administration of a strong CYP3A4 inducer, consider increasing the AFINITOR dose from 10 mg daily up to 20 mg daily (based on pharmacokinetic data), using 5 mg increments. This dose of AFINITOR is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other.
10 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with AFINITOR. The incidence of Common Toxicity Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was 4% and 0%, respectively *[see Adverse Reactions (6.1)]*. Fatal outcomes have been observed.
Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.
Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at 5 mg daily.
For cases where symptoms of non-infectious pneumonitis are severe, discontinue AFINITOR therapy and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with AFINITOR may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens *[see Adverse Reactions (6.1)]*. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR, be vigilant for signs and symptoms of infection and institute appropriate treatment promptly. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR. In the randomized study, approximately 44% of AFINITOR-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 and 2 *[see Adverse Reactions (6.1)]*. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.4 Laboratory Tests and Monitoring

Renal Function
Elevations of serum creatinine, usually mild, have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.
Blood Glucose and Lipids
Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.
Hematological Parameters
Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.5 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong or moderate inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, voriconazole, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil or diltiazem) or P-glycoprotein (PgP) should be avoided *[see Drug Interactions (7.1)]*.
An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) *[see Dosage and Administration (2.2) and Drug Interactions (7.2)]*.

5.6 Hepatic Impairment
The safety and pharmacokinetics of AFINITOR were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.
AFINITOR has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population *[see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]*.

5.7 Vaccinations
The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.8 Use in Pregnancy
Pregnancy Category D
There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in another section of the label:
- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.

- Infections *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.
The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.
The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.
Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.
Table 1 Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			**Placebo N=137**		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Any Adverse Reaction	**97**	**52**	**13**	**93**	**23**	**5**
Gastrointestinal Disorders						
Stomatitis [a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0

Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and Infestations [b]	37	7	3	18	1	0
General Disorders and Administration Site Conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis [c]	14	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and Nutrition Disorders						
Anorexia	25	1	0	14	<1	0
Nervous System Disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	10	1	0	7	0	0
Median Duration of Treatment (d)		**141**			**60**	

CTCAE Version 3.0

[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of <10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (<1%)

Nervous system disorders: Insomnia (9%), dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key treatment-emergent laboratory abnormalities are presented in Table 2.

Table 2 Key Laboratory Abnormalities Reported at a Higher rate in the AFINITOR Arm than the Placebo Arm

Laboratory Parameter	**AFINITOR 10 mg/day N=274**	**Placebo N=137**

	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical Chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

[a] Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3-and 3.5-fold, respectively.

Concomitant strong or moderate inhibitors of CYP3A4 and PgP inhibitors should not be used *[see Warnings and Precautions (5.5)]*.

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment cannot be administered *[see Dosage and Administration (2.2) and Warnings and Precautions (5.5)]*.

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.8)]*

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft) and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure (AUC_{0-24h}) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.
In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.
Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m^2) and 0.8 mg/kg (9.6 mg/m^2), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m^2).

8.3 Nursing Mothers
It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness in pediatric patients have not been established.

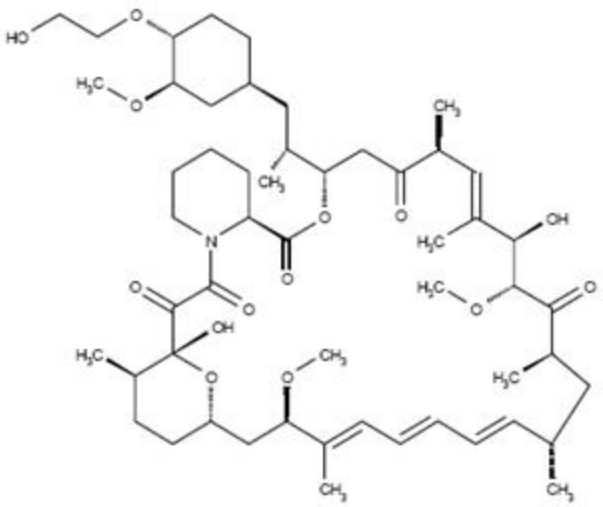
8.5 Geriatric Use
In the randomized study, 41% of AFINITOR-treated patients were ≥ 65 years in age, while 7% percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.
No dosage adjustment is required in elderly patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily *[see Dosage and Administration (2.2), Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.
The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed and use in this patient population is not recommended *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE
In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

11 DESCRIPTION
AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.
The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18- dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.
The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is



AFINITOR is supplied as tablets for oral administration containing 5 mg and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of AFINITOR in single doses up to 50 mg.

Exposure Response Relationships

Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose.

12.3 Pharmacokinetics

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within two weeks following once-daily dosing.

Food effect: Based on data in healthy subjects taking 1 mg everolimus tablets, a high-fat meal reduced C_{max} and AUC by 60% and 16%, respectively. No data are available with AFINITOR 5 mg and 10 mg tablets.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given AFINITOR 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state C_{max} following an oral dose of 10 mg daily is more than 12-fold below the Ki-values of the *in vitro* inhibition. Therefore, an effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is unlikely.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabelled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [^{14}C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25 – 178 mL/min) was detected on oral clearance (CL/F) of everolimus *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

The average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. A dose reduction for patients with Child-Pugh class B hepatic impairment is recommended. AFINITOR should not be used in patients with severe (Child-Pugh class C) hepatic impairment as the impact of severe hepatic impairment on everolimus exposure has not been assessed *[see Dosage and Administration (2.2), Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n = 6) had on average exposures that were higher than non-Japanese patients receiving the same dose.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians.

The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure ($AUC_{0\text{-}24h}$) at the recommended human dose of 10 mg daily.

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella,* mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m^2/day, approximately 255-fold the recommended human dose, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm count, and plasma testosterone levels were diminished at 5 mg/kg, which resulted in infertility at 5 mg/kg. Effects on male fertility occurred at the $AUC_{0\text{-}24h}$ values below that of therapeutic exposure (approximately 10%-81% of the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 10 mg daily). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant). Oral doses of everolimus in female rats at ≥ 0.1 mg/kg (approximately 4% the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 10 mg daily) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

An international, multicenter, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score[1] and prior anticancer therapy.

Progression-free survival (PFS), documented using RECIST (Response Evaluation Criteria in Solid Tumors) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR 10 mg daily.

In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

AFINITOR was superior to placebo for progression-free survival (see Table 3 and Figure 1). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. The overall survival (OS) results were not mature and 32% of patients had died by the time of cut-off.

Table 3 Efficacy Results by Central Radiologic Review

	AFINITOR N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value [a]
Median Progression-free Survival (95% CI)	4.9 months (4.0 to 5.5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.0001
Objective Response Rate	2%	0%	n/a [b]	n/a [b]

[a] Log-rank test stratified by prognostic score.

[b] Not applicable.

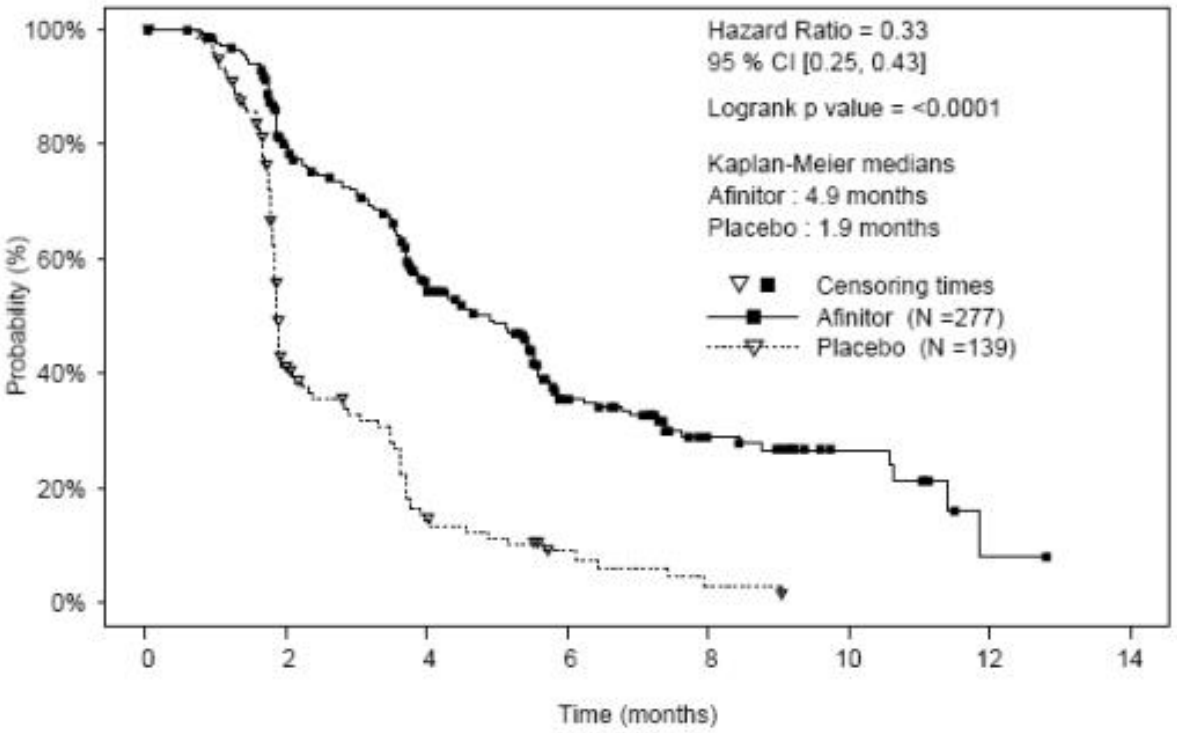


Figure 1 Kaplan-Meier Progression-free Survival Curves

15 REFERENCES

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4. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-1193.

5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

5 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other; available in:

Blisters of 28 tablets NDC 0078-0566-51

Each carton contains 4 blister cards of 7 tablets each

10 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other; available in:

Blisters of 28 tablets NDC 0078-0567-51

Each carton contains 4 blister cards of 7 tablets each

Store AFINITOR (everolimus) tablets at 25° C (77°F); excursions permitted between 15°–30°C (59°–86°F). [See USP Controlled Room Temperature.] Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-5]

AFINITOR tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed tablets.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.9)

17.1 Non-infectious Pneumonitis

Warn patients of the possibility of developing non-infectious pneumonitis. In clinical studies, some non-infectious pneumonitis cases have been severe and occasionally fatal. Advise patients to report promptly any new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

17.2 Infections

Inform patients that they may be more susceptible to infections while being treated with AFINITOR. In clinical studies, some of these infections have been severe (e.g., leading to respiratory failure) and occasionally fatal. Patients should be aware of the signs and symptoms of infection and should report any such signs or symptoms promptly to their physician *[see Warnings and Precautions (5.2)]*.

17.3 Oral Ulceration

Inform patients of the possibility of developing mouth ulcers, stomatitis and oral mucositis. In such cases, mouthwashes and/or topical treatments are recommended, but these should not contain alcohol or peroxide *[see Warnings and Precautions (5.3)]*.

17.4 Laboratory Tests and Monitoring

Inform patients of the need to monitor blood chemistry and hematology prior to the start of AFINITOR therapy and periodically thereafter *[see Warnings and Precautions (5.4)]*.

17.5 Drug-drug Interactions

Avoid concurrent treatment with strong or moderate CYP3A4 and PgP inhibitors and strong CYP3A4 and PgP inducers. If AFINITOR must be co-administered with strong CYP3A4 inducers, consider a dose increase and carefully monitor the patient for clinical response. Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Warnings and Precautions (5.5)]*.

17.6 Hepatic Impairment

Advise patients that AFINITOR is not recommended in patients with severe hepatic impairment (Child-Pugh class C). Prescribe a reduced dose of 5 mg AFINITOR per day for patients with moderate hepatic impairment (Child Pugh class B) *[see Dosage and Administration (2), Warnings and Precautions (5.6) and Clinical Pharmacology (12)]*.

17.7 Vaccinations

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines *[see Warnings and Precautions (5.7)]*.

17.8 Pregnancy

Advise female patients of childbearing potential that AFINITOR may cause fetal harm and that an effective method of contraception should be used during therapy with AFINITOR and for 8 weeks after ending treatment.

17.9 FDA-approved Patient Labeling

PATIENT INFORMATION
AFINITOR®
(a-fin-it-or)
(everolimus)

Tablets

Read this patient information leaflet before you start taking AFINITOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AFINITOR?

- **AFINITOR can cause you to have lung or breathing problems.** Tell your healthcare provider right away if you have new or worsening cough, shortness of breath, difficulty breathing, or wheezing. In some patients lung or breathing problems have been severe, and can even lead to death. You may need to stop AFINITOR for awhile or use a lower dose.

- **AFINITOR can make you more likely to have an infection** such as pneumonia or a bacterial or fungal infection. In some patients infections have been severe, and can even lead to death. You may need to be treated as soon as possible. Tell your healthcare provider right away if you have a temperature of 100.5# F or above, chills, or do not feel well.

What is AFINITOR?

AFINITOR is a prescription medicine used to treat people with advanced kidney cancer (renal cell carcinoma or RCC).

AFINITOR stops cancer cells from making new cancer cells and also cuts off the blood supply to the cancer. This may slow the growth and spread of kidney cancer.

AFINITOR has not been studied in children.

Who should not take AFINITOR?

Do not take AFINITOR if you are allergic to AFINITOR or to any of its ingredients. See the end of this leaflet for a complete list of ingredients in AFINITOR. Talk to your healthcare provider before taking this medicine if you are allergic to:

- sirolimus (Rapamune®, rapamycin)

- temsirolimus (Torisel®),

Ask your healthcare provider if you do not know.

What should I tell my healthcare provider before taking AFINITOR?

Before taking AFINITOR, tell your healthcare provider about all your medical conditions including if you:

- Have or have had liver problems.

- Have diabetes or high blood sugar.

- Have high cholesterol levels.

- Are scheduled for any immunization of a live vaccine or may be around people who have recently received an immunization with a live vaccine. If you are not sure about the type of immunization or vaccine, ask your healthcare provider.

- Are pregnant, or could become pregnant. AFINITOR may harm your pregnancy or fetus. You should use effective birth control while using AFINITOR and for 8 weeks after stopping treatment.

- Are breast-feeding or plan to breast-feed. It is not known if AFINITOR passes into your breast milk. You and your healthcare provider should decide if you will take AFINITOR or breast-feed. You should not do both.

How does AFINITOR impact your childbearing potential?

- AFINITOR may decrease male and female fertility.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

AFINITOR can affect the way other medicines work, and other medicines can affect how AFINITOR works. Using AFINITOR with other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine. Especially tell your healthcare provider if you take:

- St. John’s Wort (also known as *Hypericum perforatum*)

- Medicine for:
- Fungal infections
- Bacterial infections
- Tuberculosis
- Seizures
- HIV-AIDS
- Heart conditions or high blood pressure
- Immunosuppression

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of those taken for the conditions listed above. If you are taking any medicines for the conditions listed above, your healthcare provider might need to prescribe a different medicine. You should also tell your healthcare provider before you start taking any new medicine.

How should I take AFINITOR?

AFINITOR comes in 5 mg and 10 mg tablets.

- Take AFINITOR exactly as your healthcare provider tells you.
- Swallow AFINITOR tablets whole with a glass of water. Do not crush or chew the tablets. If you cannot swallow AFINITOR tablets whole, tell your healthcare provider.
- Take AFINITOR each day, at about the same time, with or without food.
- If you take too much AFINITOR contact your healthcare provider or go to the nearest hospital emergency department right away. Take the pack of AFINITOR with you.
- If you miss a dose of AFINITOR, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your AFINITOR, skip the dose for that day. The next day, take AFINITOR at your usual time. Do not take 2 doses to make up for the one that you missed. If you are not sure about what to do, call your healthcare provider.
- You will have regular blood tests before you start and during your treatment with AFINITOR. These tests will show the number of blood cells in your body to see if AFINITOR is having an unwanted effect on these cells. Also, blood tests will monitor how your kidneys and liver are working and your blood sugar levels.

What should I avoid while taking AFINITOR?

- Do not drink grapefruit juice or eat grapefruit during your treatment with AFINITOR. It may make the amount of AFINITOR in your blood increase to a harmful level.

What are the possible side effects of AFINITOR?

AFINITOR can cause serious side effects. See the, "What is the most important information I should know about AFINITOR?" section at the beginning of this leaflet.

Common side effects:

- **Mouth ulcers.** AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. You might need treatment with a special mouthwash or mouth gel. Ask your healthcare provider what type of mouthwash or mouth gel to use.
- **Infections**
- **Feeling weak or tired**
- **Cough, shortness of breath, and lung or breathing problems**
- **Diarrhea**
- **Rash, dry skin, and itching**
- **Nausea and vomiting**
- **Fever**
- **Loss of appetite**
- **Swelling of arms, hands, feet, ankles, face or other parts of the body**
- **Abnormal taste**
- **Inflammation of lining of the digestive system**
- **Headache**
- **Nose bleeds**
- **Pain in arms and legs**

Tell your healthcare provider if you have any side effect that bothers you or does not go away.
These are not all the possible side effects of AFINITOR. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store AFINITOR?

- Keep AFINITOR at room temperature, between 59° to 86°F (15° to 30°C).
- Keep AFINITOR in the original package.
- Open blister package just before taking AFINITOR; use scissors to open blister.
- Keep the package and tablets dry.
- Keep AFINITOR out of light.
- Safely throw away AFINITOR that is out of date or no longer needed.

Keep this and all medicines out of the reach and sight of children.

General information about AFINITOR

Medicines are sometimes prescribed for conditions that are not mentioned in this patient information leaflet. Do not use AFINITOR for a condition for which it was not prescribed.
Do not give AFINITOR to other people, even if they have the same problem you have. It may harm them.
This leaflet summarizes the most important information about AFINITOR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information written for healthcare professionals.
For more information call 1-888-423-4648.

What are the ingredients in AFINITOR?

Active ingredient: everolimus.
Inactive ingredients: butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.
The brands listed are the trademarks or register marks of their respective owners and are not trademarks or register marks of Novartis.
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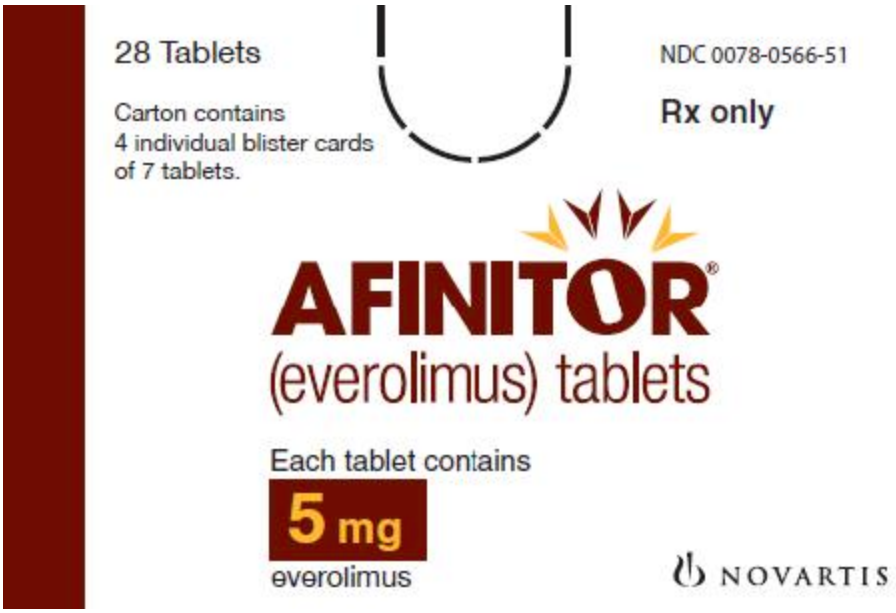
Novartis Pharma Stein AG
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
MARCH 2009 T2009-14/T2009-15

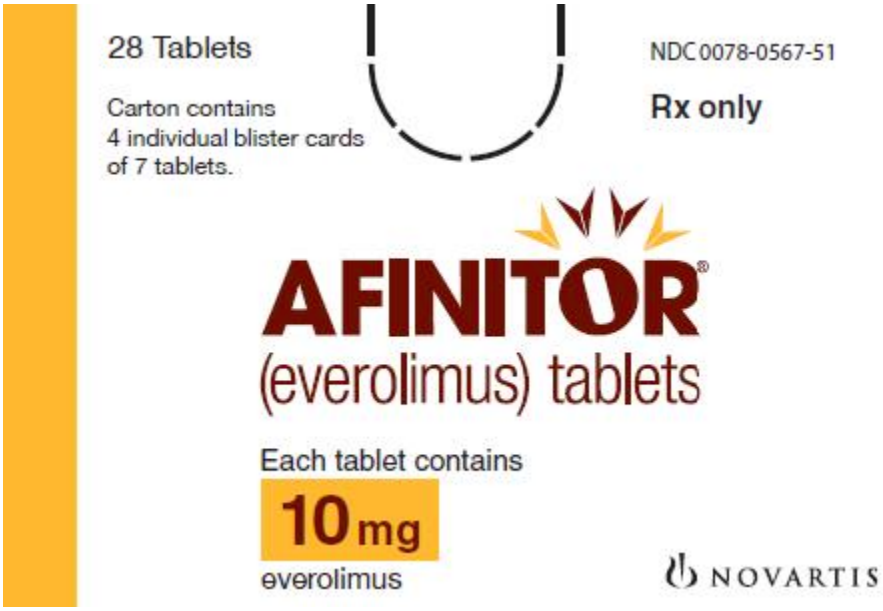
PRINCIPAL DISPLAY PANEL

Package Label – 5 mg

Rx Only NDC 0078-0566-51
Afinitor® (everolimus) Tablets
Each tablet contains
5 mg everolimus
28 Tablets
Carton contains 4 individual blister cards of 7 tablets.



PRINCIPAL DISPLAY PANEL
Package Label – 10 mg
Rx Only NDC 0078-0567-51
Afinitor® (everolimus) Tablets
Each tablet contains
10 mg everolimus
28 Tablets
Carton contains 4 individual blister cards of 7 tablets.



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